ELSEVIER

Toxicology 160 (2001) 173–180

TOXICOLOGY

www.elsevier.com/locate/toxicol

Factors modulating the epithelial response to toxicants in tracheobronchial airways

C.G. Plopper *, A. Buckpitt, M. Evans, L. Van Winkle, M. Fanucchi, S. Smiley-Jewell, J. Lakritz, J. West, G. Lawson, R. Paige, L. Miller, D. Hyde

VM: Anatomy, Physiology and Cell Biology, School of Veterinary Medicine, University of California, Davis, CA 95616, USA

Abstract

As one of the principal interfaces between the organism and the environment, the respiratory system is a target for a wide variety of toxicants and carcinogens. The cellular and architectural complexity of the respiratory system appears to play a major role in defining the focal nature of the pulmonary response to environmental stressors. This review will address the biological factors that modulate the response of one of the major target compartments within the respiratory system, the tracheobronchial airway tree. Individual airway segments respond uniquely to toxic stress and this response involves not only the target cell population, e.g. epithelium, but also other components of the airway wall suggesting a trophic interaction within all components of the airway wall in maintaining steady state and responding to injury. A number of biological factors modulate the nature of the response, including: (1) metabolic potential at specific sites for activation and detoxification; (2) the nature of the local inflammatory response; (3) age of the organism at the time of exposure; (4) gender of the exposed organism; (5) history of previous exposure; and (6) species and strain of the organism exposed.

1. Introduction

The respiratory system is exposed to a wide variety of environmental contaminants. The cellular and architectural complexity of this system establishes a wide range of microenvironments with different cellular composition and response to environmental stressors. The variable nature of the response is consistent regardless of whether the route of exposure is via inhaled air or the vascular system. More than 40 cell phenotypes found in the lungs are not uniform either in their distribution throughout the organ or in their response to toxicants. This is especially true for target cell populations that occupy the tracheobronchial airway tree. Increasing evidence strongly suggests that cell populations within the tracheobronchial airways establish distinct microenvironments that vary markedly in their steady state biological activity and in their potential for response to environmental stressors. The composition of the entire airway wall appears to contribute to the steady state function of all of the cell populations within the local environment. In addition, all the cell populations appear to respond to stress even when only one subpopulation

* Corresponding author. Tel.: +1-530-752-1174.

0300-483X/01/$ - see front matter
PII: S0300-483X(00)00453-4

is targeted. This discussion will first address the concept of the organization of an airway wall as a microenvironment of complex cellular and acellular composition with strong trophic interactions. In addition, the current state of our understanding of the biological factors, which modulate the response of these individual microenvironments as targets of toxic injury, will be defined.

2. Epithelial–mesenchymal trophic unit as a paradigm

The concept of the epithelial–mesenchymal trophic unit was developed as a framework for defining the cellular and metabolic mechanisms regulating the response to toxic injury in a complex biological structure such as the tracheobronchial airway tree (Evans et al., 1999; Holgate, 2000). Each segment, or airway generation, within the branching pattern is addressed as a unique biological entity whose properties may differ from those of neighboring branches. The portions of the airways between branch points are treated as separate biological entities from each other and from the intervening branch points. All the components of the airway wall, both cellular and acellular, are assumed to play a role in both injury and repair responses (Fig. 1). The epithelial compartment of the airway wall is comprised of surface epithelium and submucosal glands. The interstitial compartment includes the basement membrane zone, fibroblasts, including the attenuated fibroblast sheath beneath the basement membrane, smooth muscle, cartilage and the vasculature. The nervous compartment includes the nerve processes which interdigitate between the smooth muscle, the subepithelial matrix and the epithelium. This includes both afferent and efferent limbs of the nervous system and the central regulating neurons in the brain stem. The immunological compartment includes both inflammatory cells and migratory cells involved in regulation of immune responses. The basic assumption is that all of these compartments have an active interaction with each other, i.e. the biological function of a cell in one compartment is regulated by the functions of the cell populations in the other compartments. In the steady state these compartments establish a baseline trophic interaction that is disrupted during acute injury and repair and is reset by successive cycles of injury, inflammation and repair characteristic of chronic airway diseases.

Perturbation of one compartment creates an imbalance in all compartments, or rather; a metabolic response in one compartment will produce alterations in the other compartments (Evans et al., 1999; Holgate, 2000). This paradigm in chronic injury or inflammatory airway diseases such as chronic bronchitis or asthma, indicates that disease manifests itself as a complete alteration of not only the cellular compartments directly involved in the interface with injurants or allergens, but also in marked changes in the other compartments (e.g. induction of myofibroblasts, smooth muscle hypertrophy, interstitial fibrosis and thickening of the basement membrane zone; Paige and Plopper, 1999).

3. Modulating factors

Using the concept that the cellular population which organizes a conducting airway as a biological entity unique to a particular branch of the airway tree emphasizes the number of factors by which they differ in their pathobiological response to toxic injury, including susceptibility to acute injury, the pattern of repair and the development of tolerance. Issues to be considered include: airway microenvironment, the status of differentiation based on animal age, the history of previous exposure to injurants and the impact of differences in species and strain.

3.1. Airway microenvironment

There are two aspects of microenvironment that are critical when defining the pathobiology of the response to injury. The first is that all the cellular populations in the airway wall are vital for maintaining differentiated function of the epithelium (Van Winkle et al., 1996a). The three-dimensional configuration of the airway, in other words an intact tubular structure including all components

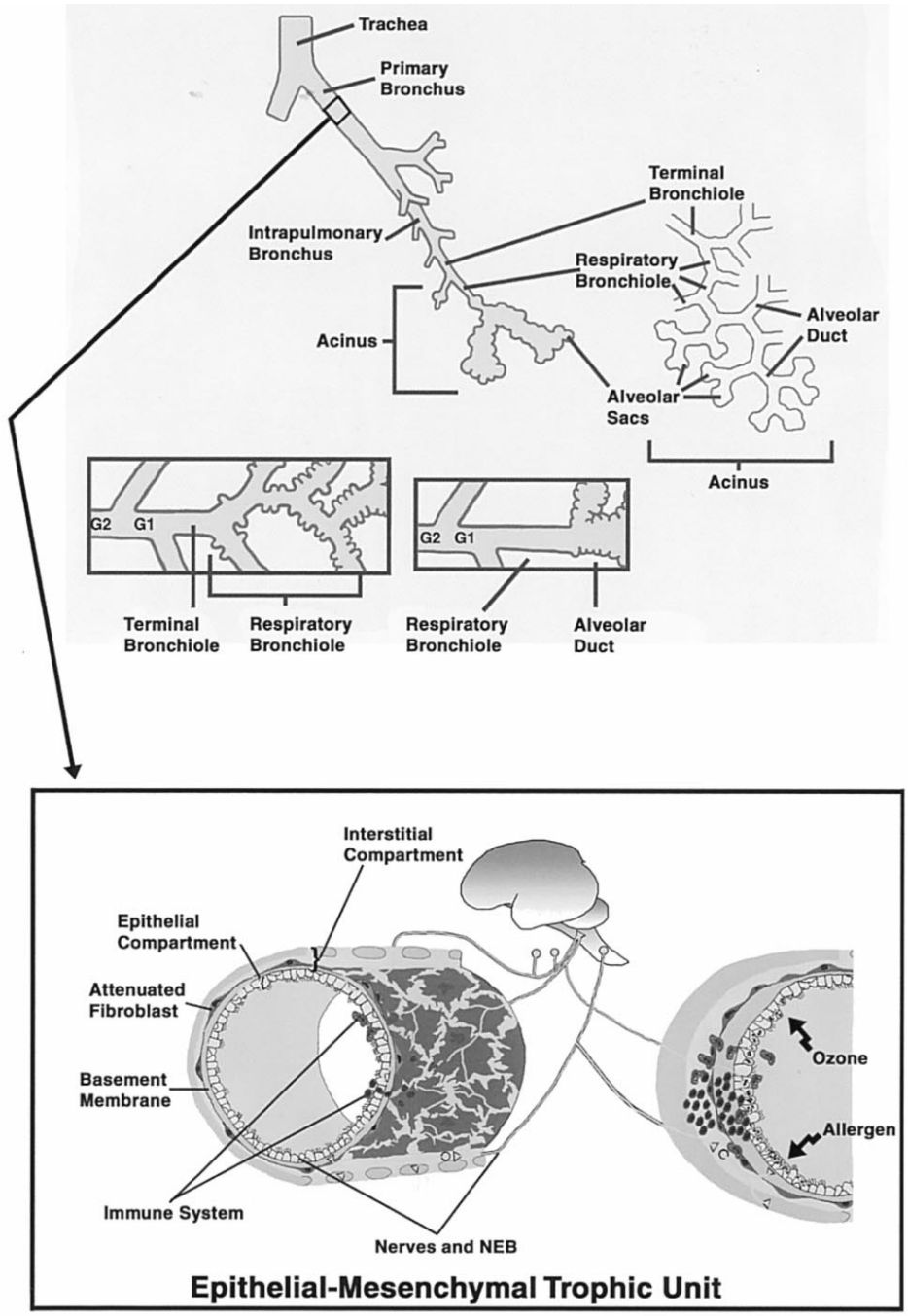

Fig. 1. Diagrammatic representation of the epithelial–mesenchymal trophic unit and its relationship to the tracheobronchial airway tree. The parts of the tracheobronchial airways include the bronchi, bronchioles and the acinus, the functional unit of the gas exchange area. There is considerable variation in the organization of the transition zone between the conducting airways and the gas exchange area. In many species, the transition is abrupt with terminal bronchioles opening directly into alveolar ducts, while in other species the transition between terminal bronchioles and alveolar ducts is extensive with a number of generations of alveolarized (respiratory) bronchioles intervening. The epithelial–mesenchymal trophic unit includes interactions between all compartments of the airway wall, epithelium, fibroblasts, basement membrane zone, cells of the immune system, nerve fibers and neuroendocrine cells.

of the wall, is necessary. The absence of an open tubular structure due to collapse or rupture of airway wall integrity results in a transformation of the epithelial populations. In addition, the entire repair process after acute injury, including proliferation, migration to reestablish cell density and differentiation of epithelial phenotypes, will occur in vitro in intact airways under normal growth conditions independent of the animal (Van Winkle et al., 1996b).

The second feature is that the injury response varies markedly by the position of the target cells within the tracheobronchial airway tree (Mariassy et al., 1992; Plopper and Hyde, 1992; Plopper, 1993; Pinkerton et al., 1997; Paige and Plopper, 1999). This is true for a wide variety of chemicals, including oxidant gases (Hyde et al., 1992; Plopper et al., 1998; Paige and Plopper, 1999) and bioactivated hydrocarbons (Plopper et al., 1992a,b; Paige et al., 1997). Regardless of the chemical or the phenotype of the target cell population, the sensitivity varies widely between proximal and distal airways. This is also true whether the injury generates an inflammatory response or not.

3.2. Airway microenvironment and metabolism

Once it is recognized that the injury response of even contiguous epithelial populations in different airway generations is different, an analysis of potential mechanisms which modulate these differing patterns of susceptibility identifies a wide variety of factors which play a role in modulating these differences. Modulation of non-enzymatic cofactors, such as glutathione, varies by the position of the cells within the airway tree, including steady state concentrations of intracellular glutathione, response to depletion, and patterns of reestablishment of the pool under stress conditions (Duan et al., 1996; Plopper et al., 1998; West et al., 2000). All of the enzymes recognized as participating in pathways which detoxify, neutralize, or conjugate reactive compounds within cells, for instance, glutathione *S*-transferase, glutathione peroxidase, superoxide dismutase and catalase, all vary widely in their enzymatic activity depending on position within the airway tree (Duan et al., 1993; Buckpitt et al., 1995). For bioactivated compounds, the metabolic potential for target cells to activate these compounds to reactive intermediates also varies widely depending on position within the airway tree (Buckpitt et al., 1992; Franklin et al., 1993; Buckpitt et al., 1995; Buckpitt and Cruikshank, 1997; Watt et al., 1998).

3.3. Airway microenvironment and inflammation

An additional factor is that the inflammatory response to acute epithelial injury also appears to be unique to the cell populations residing in specific airway generations. Immune cell accumulation within the lung occurs as the result of either an acute injury or a chronic disease process. Differential distribution of leukocytes, antigen presenting cells, and inflammatory/immune mediators throughout the lung should be expected based on the distinct microenvironments presented by each airway generation. The unique cellular and matrix constituents of each branch of the airway tree present a complex recognition pattern that can promote local recruitment or expansion of highly specific leukocyte subpopulations into these areas. Immune cells and their associated mediators can be further compartmentalized within each airway generation by lumen, epithelium, and interstitium; luminal accruement of cells/mediators may also vary between different lung lobes. Surprisingly, there has been little evidence reported to support this notion. Site-specific leukocyte trafficking is further complicated by numerous forms of pulmonary injury and disease that initiate the development of an inflammatory/immune response. Hyde et al. (1992, 1999) have shown that short-term acute ozone inhalation results in a time-dependent pattern of epithelial cell injury, accompanied by granulocyte recruitment that is distinct for both specific airway generations and compartments (i.e. epithelium versus interstitium). In another report, comparative analysis of patients with severe asthma and cystic fibrosis has indicated that the distribution of CD45+ cells and eosinophils within mucosal and submucosal compartments of large versus small airways is variable in disease-specific manner (Haley et al.,

1998). It is apparent from these studies that definition of compartments and airway generations for immune cells can define a pathological process in the lung. As such, precise localization of the mucosal immune system throughout lung could have important implications with respect to development of appropriate immunomodulatory therapeutics that target specific pulmonary disease states.

3.4. Age

The age of the animals at the time of exposure to injurants plays a tremendous role in the pattern of injury and repair (Fanucchi and Plopper, 1997). This is especially true for very young animals in the early postnatal period when the respiratory system is completing its growth and maturation. Infants are much more susceptible to injury by bioactivated lung toxicants than are adults of the same species, even at doses below the no-effect level for adults (Plopper et al., 1994; Fanucchi et al., 1997a,b; Smiley-Jewell et al., 2000). This appears to be closely tied to the differentiation of target cell population and the induction of relevant enzyme systems (Plopper et al., 1993; Gebremichael et al., 1995; Ji et al., 1995; Fanucchi and Plopper, 1997). A pattern of differential expression for detoxification systems also shows a time-dependent pattern of expression during postnatal lung development and could represent the pronounced mismatches between activation potential and detoxification potential which could account for the elevated susceptibility of infants (Fanucchi et al., 2000). There appear to be critical time points during the period of postnatal lung development in infants where this susceptibility is much higher than others (Plopper et al., 1994; Fanucchi et al., 1997a; Smiley-Jewell et al., 2000). Another impact of age, especially as it is related to the postnatal lung development of infants, is the failure of acute epithelial injury in tracheobronchial airways to repair (Fanucchi et al., 1997a; Smiley-Jewell et al., 1998, 2000). Injury to young animals results in cessation of the cycle of repair in the proliferative and squamation phases, surviving cuboidal cells do not differentiate and squamated survivors do not recover to a cuboidal epithelial pattern. Also epithelial cell density markedly reduced. This arrangement of the airway epithelium persists for significant periods of time into adulthood.

3.5. Gender

The role which gender plays in modulating pulmonary responses to toxicants is largely unknown. Gender has been shown to be a factor in human lung disease, particularly in lung cancer (Baldini and Strauss, 1997) and in airway hyperresponsiveness (Gold et al., 1994). In addition, autoimmune diseases affect women disproportionately (Jacobson et al., 1997; Whitacre et al., 1999). Gender is related, in experimental animals, to differences in various X-linked genes, hormone regulated receptors and enzymes, metabolism and detoxification of xenobiotics and susceptibility to long-term lung remodeling such as lung fibrosis and cancer. For instance, sensitivity to bleomycin induced lung fibrosis varies not only by strain of mouse but also substantially by gender with female C57BL/6J mice being more resistant to fibrosis than males of the same strain (Haston et al., 1996). The metabolic mechanisms that underlie differential susceptibility by gender may be due to differences in activity or abundance of various cytochrome P450 isozymes (Guo et al., 1993; Elfarra et al., 1998), inducibility of P450 isozymes (Paolini et al., 1995), levels of GST isoenzymes (Mitchell et al., 1997; Singh et al., 1998), GSH levels (Flagg et al., 1993), or still undefined differences between male and female metabolism with the lung itself as well as in other tissues. The basis for differences in long-term cellular repair responses remains unknown. However, various X-linked genes, hormone-regulated receptors and enzymes are likely to play a role. Unfortunately, there have been few animal models that examine the effect of gender on lung injury and even fewer that evaluate long-term repair responses. Many basic issues remain unanswered including the pattern and degree of acute lung injury, the duration and completeness of repair, the impact of repeated exposures, the regulatory elements involved in repair and the role of various cell types.

3.6. History of exposure

Exposure to the same injurant on a repeated basis alters the acute injury response, the pattern of inflammation and the end result of repair (Plopper, 1993; Lakritz et al., 1996; Paige and Plopper, 1999). Repeated exposure that occurs while the process of repair from initial acute injury is ongoing reduces the level of susceptibility of target cell populations to further injury. Extending the interexposure period past the time frame necessary to completely repair acute injury has the opposite effect. The continual cycles of injury and repair result in larger, more pronounced alterations in both matrix and epithelial populations. This is true both for exposure to oxidant gases and bioactivated hydrocarbons. Each population residing in different generations of tracheobronchial airways respond to repeated exposure injury and repair cycles by different patterns.

3.7. Species and strain

Comparison of acute injury responses and subsequent repair in different species has established that the patterns are unique for the species under consideration and that even cells occupying identical airway positions in different species respond differently (Plopper, 1993; Hahn, 1997; Kodavanti and Costa, 1999; Paige and Plopper, 1999). For a wide range of bioactivated compounds and some oxidant gases, different species have different dose responses to exposure and this varies by position within the airway tree (Plopper, 1993; Paige and Plopper, 1999). The relative differences in susceptibility between species for a particular chemical will not necessarily apply to additional chemicals, even of the same class. While it appears that injured epithelial cells in different species follow the same general pattern of repair, the timing and extent of each phase also appears to be species specific. The complexity of differences between species in injury and repair is also found in different strains of mice (Warheit, 1989; Henry et al., 1993; Kleeberger, 1995; Slade et al., 1997; Wesselkamper et al., 2000); whether this includes the relative susceptibility to injury by populations in different portions of the airway tree and in the rates and extent of the different phases of repair is not clear.

References

Baldini, E.H., Strauss, G.M., 1997. Women and lung cancer: waiting to exhale. Chest 112, 229S–243S.

Buckpitt, A., Buonarati, M., Bahnson Avey, L., Min Chang, A., Morin, D., Plopper, C., 1992. Relationship of cytochrome P-450 activity to Clara cell cytotoxicity. II. Comparison of stereoselectivity of naphthalene epoxidation in lung and nasal mucosa of mouse, hamster, rat and rhesus monkey. J. Phar. Exper. Ther. 261 (1), 364–372.

Buckpitt, A., Chang, A.-M., Weir, A., Van Winkle, L., Duan, X., Philpot, R., Plopper, C., 1995. Relationship of cytochrome P450 activity to Clara cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. Mol. Pharmacol. 47, 74–81.

Buckpitt, A.R., Cruikshank, M.K., 1997. Biochemical function of the respiratory tract: metabolism of xenobiotics. In: Sipes, I.G., McQueen, C.A., Gandolfi, A.J. (Eds.), Comprehensive Toxicology: Toxicology of the Respiratory System. Elsevier, Amsterdam, pp. 160–186.

Duan, X., Buckpitt, A.R., Plopper, C.G., 1993. Variation in antioxidant enzyme activities in anatomic subcompartments within rat and rhesus monkey lung. Toxicol. Appl. Pharmacol. 123, 73–82.

Duan, X., Plopper, C., Brennan, P., Buckpitt, A., 1996. Rates of glutathione synthesis in lung subcompartments of mice and monkeys: possible role in species and site selective injury. J. Pharmacol. Exp. Ther. 277, 1402–1409.

Elfarra, A.A., Krause, R.J., Last, A.R., Lash, L.H., Parker, J.C., 1998. Species- and sex-related differences in metabolism of trichloroethylene to yield chloral and trichloroethanol in mouse, rat, and human liver microsomes. Drug Metab. Dispos. 26, 779–785.

Evans, M.J., Van Winkle, L.S., Fanucchi, M.V., Plopper, C.G., 1999. The attenuated fibroblast sheath of the respiratory tract epithelial–mesenchymal trophic unit. Am. J. Resp. Cell Mol. Biol. 21, 655–657.

Fanucchi, M.V., Buckpitt, A.R., Murphy, M.E., Plopper, C.G., 1997a. Naphthalene cytotoxicity of differentiating Clara cells in neonatal mice. Toxicol. Appl. Pharmacol. 144, 96–104.

Fanucchi, M.V., Plopper, C.G., 1997. Pulmonary developmental responses to toxicants. In: Sipes, I.G., McQueen, C.A., Gandolfi, A.J. (Eds.), Comprehensive Toxicology: Toxicology of the Respiratory System, vol. 8. Pergamon Press, Oxford, pp. 203–220.

Fanucchi, M.V., Murphy, M.E., Buckpitt, A.R., Philpot, R.M., Plopper, C.G., 1997b. Pulmonary cytochrome P450 monooxygenase and Clara cell differentiation in mice. Am. J. Resp. Cell Mol. Biol. 17, 302–314.

Fanucchi, M.V., Buckpitt, A.R., Murphy, M.E., Storms, D.H., Hammock, B.D., Plopper, C.G., 2000. Development of phase II xenobiotic metabolizing enzymes in differentiating murine Clara cells. Tox. Appl. Pharmacol. 168, 253–267.

Flagg, E.W., Coates, R.J., Jones, D.P., Eley, J.W., Gunter, E.W., Jackson, B., Greenberg, R.S., 1993. Plasma total glutathione in humans and its association with demographic and health-related factors. Br. J. Nutr. 70, 797–808.

Franklin, R.B., Plopper, C.G., Buckpitt, A.R., 1993. Naphthalene and 2-methylnaphthalene-induced pulmonary bronchiolar epithelial cell necrosis: metabolism and relationship to toxicity. In: Gram, T.E. (Ed.), Metabolic Activation and Toxicity of Chemical Agents to Lung Tissue and Cells, Section 138, vol. 7. Pergamon Press, UK, pp. 123–144 Chapter 7.

Gebremichael, A., Chang, A.M., Buckpitt, A.R., Plopper, C.G., Pinkerton, K.E., 1995. Postnatal development of cytochrome P4501A1 and 2B1 in rat lung and liver: effect of aged and diluted sidestream cigarette smoke. Toxicol. Appl. Pharmacol. 135, 246–253.

Gold, D.R., Wypij, D., Wang, X.B., Speizer, F.E., Pugh, M., Ware, J.H., Ferris, B.G., Dockery, D.W., 1994. Gender- and race-specific effects of asthma and wheeze on level and growth of lung function in children in six US cities. Am. J. Respir. Crit. Care Med. 149 (5), 1198–1208.

Guo, Z.Y., Wang, M.H., Tian, G., Burger, J., Gochfeld, M., Yang, C.S., 1993. Age- and gender-related variations in the activities of drug-metabolizing and antioxidant enzymes in the white-footed mouse (*Peromyscus leucopus*). Growth Dev. Aging 57, 85–100.

Hahn, F.F., 1997. Carcinogenic responses of the respiratory tract. In: Sipes, I.G., McQueen, C.A., Gandolfi, A.J. (Eds.), Comprehensive Toxicology of the Respiratory System. Elsevier, Amsterdam, pp. 187–201.

Haley, K.J., Sunday, M.E., Wiggs, B.R., Kozakewich, H.P., Reilly, J.J., Mentzer, S.H., Sugarbaker, D.J., Doerschuk, C.M., Drazen, J.D., 1998. Inflammatory cell distribution within and along asthmatic airways. Am. J. Res. Crit. Care Med. 158, 565–572.

Haston, C.K., Amos, C.I., King, T.M., Travis, E.L., 1996. Inheritance of susceptibility to bleomycin-induced pulmonary fibrosis in the mouse. Cancer Res. 56, 2596–2601.

Henry, M., McArthur, M., Montgomery, C., Bradley, A., Donehower, A., 1993. Genetic background alters the spectrum of tumors that develop in p53-deficient mice. FASEB J. 7, 938–943.

Holgate, S.T., 2000. Epithelial damage and response. Clin. Exp. Allergy 30 (Suppl. 1), 37–46.

Hyde, D.M., Hubbard, W.C., Wong, V., Wu, R., Pinkerton, K., Plopper, C.G., 1992. Ozone-induced acute tracheobronchial epithelial injury: relationship to granulocyte emigration in the lung. Am. J. Respir. Cell Mol. Biol. 6, 481–497.

Hyde, D.M., Miller, L.A., McDonald, R.J., Stovall, M.Y., Wong, V., Pinkerton, K.E., Wegner, C.D., Rothlein, R., Plopper, C.G., 1999. Neutrophils enhance clearance of necrotic epithelial cells in ozone-induced lung injury in rhesus monkeys. Am. J. Physiol.: Lung Cell. Mol. Physiol. 277 (21), L1190–L1198.

Jacobson, D.L., Gange, S.J., Rose, N.R., Graham, N.M.H., 1997. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin. Immunol. Immunopathol. 84, 223–243.

Ji, C.M., Cardoso, W.V., Gebremichael, A., Philpot, R.M., Buckpitt, A.R., Plopper, C.G., Pinkerton, K.E., 1995. Pulmonary cytochrome P-450 monooxygenase system and Clara cell differentiation in rats. Am. J. Physiol.: Lung Cell. Mol. Physiol. 269 (13), L394–L402.

Kleeberger, S., 1995. Genetic susceptibility to ozone, exposure. Toxicol. Lett. 82–83, 295–300.

Kodavanti, U.P., Costa, D.L., 1999. Animal models to study for pollutant effects. In: Holgate, S.T., Samet, J.M., Koren, H.S., Maynard, R.L. (Eds.), Air Pollution and Health. Academic Press, New York, pp. 165–197.

Lakritz, J., Chang, A., Weir, A., Nishio, S., Hyde, D., Philpot, R., Buckpitt, A., Plopper, C., 1996. Cellular and metabolic basis of Clara cell tolerance to mulitple doses of cytochrome P450-activated cytotoxicants. Bronchiolar epithelial reorganization and expression of cytochrome P450 monooxygenases in mice exposed to multiple doses of naphthalene. J. Pharmacol. Exp. Ther. 278, 1408–1418.

Mariassy, A.T., 1992. Epithelial cells of trachea and bronchi. In: Parent, R.A. (Ed.), Comparative Biology of the Normal Lung. Treatise on Pulmonary Toxicology, vol. 1. CRC Press, Boca Raton, pp. 63–76.

Mitchell, A.E., Morin, D., Lakritz, J., Jones, A.D., 1997. Quantitative profiling of tissue- and gender-related expression of glutathione *S*-transferase isoenzymes in the mouse. Biochem. J. 325, 207–216.

Paige, R., Wong, V., Plopper, C., 1997. Dose-related airway-selective epithelial toxicity of 1-nitro-naphthalene in rats. Toxicol. Appl. Pharmacol. 147, 224–233.

Paige, R.C., Plopper, C.G., 1999. Acute and chronic effects of ozone in animal models. In: Holgate, S.T., Samet, J.M., Koren, H.S., Maynard, R.L. (Eds.), Air Pollution and Health. Academic Press, New York, pp. 531–557.

Paolini, M., Mesirca, R., Pozzetti, L., Sapone, A., Cantelli-forti, G., 1995. Induction of CYP2B1 mediated pentoxyresorufin O-dealkylase activity in different species, sex and tissue by prototype 2B1-inducers. Chem. Biol. Interact. 95, 127–139.

Pinkerton, K.E., Avadhanam, K.P., Peake, J.L., Plopper, C.G., 1997. Tracheobronchial airways. In: Sipes, I.G., McQueen, C.A., Gandolfi, A.J. (Eds.), Comprehensive Toxicology: Toxicology of the Respiratory System, vol. 8. Pergamon Press, Oxford, pp. 23–44.

Plopper, C.G., Hyde, D.M., 1992. Epithelial cells of bronchioles. In: Parent, R.A. (Ed.), Comparative Biology of the Normal Lung. Treatise on Pulmonary Toxicology. CRC Press, Boca Raton, pp. 85–92.

Plopper, C.G., Macklin, J., Nishio, S.J., Hyde, D.M., Buckpitt, A.R., 1992a. Relationship of cytochrome P-450 activ-

ity to Clara cell cytotoxicity. III. Morphometric comparison of changes in the epithelial populations of terminal bronchioles and lobar bronchi in mice, hamsters, and rats after parenteral administration of naphthalene. Lab. Invest. 67 (5), 553–565.

Plopper, C.G., Suverkropp, C., Morin, D., Nishio, S., Buckpitt, A., 1992b. Relationship of cytochrome P-450 activity to Clara cell cytotoxicity. 1. Histopathologic comparison of the respiratory tract of mice, rats and hamsters after parenteral administration of naphthalene. J. Pharmacol. Exp. Ther. 261 (1), 353–363.

Plopper, C.G., Weir, A.J., Morin, D., Chang, A., Philpot, R.M., Buckpitt, A.R., 1993. Postnatal changes in the expression and distribution of pulmonary cytochrome P450 monooxygenases during Clara cell differentiation in rabbits. Mol. Pharmacol. 44, 51–61.

Plopper, C., 1993. Pulmonary bronchiolar epithelial cytotoxicity: microanatomical considerations. In: Gram, T.E. (Ed.), Metabolic Activation and Toxicity of Chemical Agents to Lung Tissue and Cells. Permagon Press, UK, pp. 1–24.

Plopper, C.G., Weir, A.J., Nishio, S.J., Chang, A., Voit, M., Philpot, R.M., Buckpitt, A.R., 1994. Elevated susceptibility to 4-ipomeanol cytotoxicity in immature Clara cells of neonatal rabbits. J. Pharmacol. Exp. Ther. 269 (2), 867–880.

Plopper, C.G., Hatch, G.E., Wong, V., Duan, X., Weir, A.J., Tarkington, B.K., Devlin, R.B., Becker, S., Buckpitt, A.R., 1998. Relationship of inhaled ozone concentration to acute tracheobronchial epithelial injury, site-specific ozone dose, and glutathione depletion in rhesus monkeys. Am. J. Resp. Cell Mol. Biol. 19, 387–399.

Singh, S.V., Benson, P.J., Hu, X., Pal, A., Xia, H., Srivastava, S.K., Awasthi, S., Zaren, H.A., Orchard, J.L., Awasthi, Y.C., 1998. Gender-related differences in susceptibility of A/J mouse to benzo[a]pyrene-induced pulmonary and forestomach tumorigenesis. Cancer Lett. 128, 197–204.

Slade, R., Watkinson, W., Hatch, G., 1997. Mouse strain differences in ozone dosimetry and body temperature changes. Am. J. Physiol. 272, L73–L77.

Smiley-Jewell, S.M., Nishio, S.J., Weir, A.J., Plopper, C.G., 1998. Neonatal Clara cell toxicity by 4-ipomeanol alters bronchiolar organization in adult rabbits. Am. J. Physiol.: Lung Cell. Mol. Physiol. 274 (18), L485–L498.

Smiley-Jewell, S.M., Liu, F.J., Weir, A.J., Plopper, C.G., 2000. Acute injury to differentiating Clara cells in neonatal rabbits results in age-related failure of bronchiolar epithelial repair. Toxicol. Pathol. 28 (2), 267–276.

Van Winkle, L.S., Buckpitt, A.R., Plopper, C.G., 1996a. Maintenance of differentiated murine Clara cells in microdissected airway cultures. Am. J. Respir. Cell Mol. Biol. 14, 586–598.

Van Winkle, L.S., Isaac, J.M., Plopper, C.G., 1996b. Repair of naphthalene-injured microdissected airways in vitro. Am. J. Respir. Cell Mol. Biol. 15, 1–8.

Warheit, D., 1989. Interspecies comparisons of lung responses to inhaled particles and gas. Crit. Rev. Toxicol. 20, 1–29.

Watt, K.C., Plopper, C.G., Weir, A.J., Tarkington, B., Buckpitt, A.R., 1998. Cytochrome P450 2E1 in rat tracheobronchial airways: response to ozone exposure. Toxicol. Appl. Pharmacol. 149, 195–202.

Wesselkamper, S., Prows, D., Biswas, P., Willeke, K., Bingham, E., Leikauf, G., 2000. Genetic susceptibility to irritant-induced acute lung injury in mice. Am. J. Physiol. 279, L575–L582.

West, J.A., Buckpitt, A.R., Plopper, C.G., 2000. Elevated airway GSH resynthesis confers protection to Clara cells from naphthalene injury in mice made tolerant by repeated exposures. J. Pharm. Exp. Ther. 294, 516–523.

Whitacre, C.C., Reingold, S.C., O'Looney, P.A., 1999. Biomedicine: a gender gap in autoimmunity. Science 283, 1277–1278.